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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/817,748 | 03/26/2001 | Steven M. Tracy | UNMC 63116-CIP/13292-0004 | 7857 |

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| EXAMINER | |
|---|---|
| GUZO, DAVID | |
| **ART UNIT** | **PAPER NUMBER** |
| 1636 | 14 |

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/817,748 | Applicant(s) TRACY, STEVEN M. | |
|---|---|---|---|
| | Examiner David Guzo | Art Unit 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *09 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *16-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

**Detailed Action**

Applicants' election of Group II, claims 16-29, without traverse in Paper # 13, is acknowledged. Applicants have canceled non-elected claims 1-15.

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: Priority for the PCT/US98/04291 is claimed under 35 USC 119(a)-(d) rather than 35 USC 120.

Priority for the claimed invention is granted back to the filing date (3/26/01) of the instant application.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject

matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants claim compositions for treatment of individuals for IDDM, comprising recombinant viral vectors comprising a attenuated coxsackievirus genome which further comprises at least one expressible heterologous sequence encoding an immunomodulatory protein (i.e. IL-4). Applicants also claim methods for treating, preventing or suppressing the onset of IDDM in humans comprising administering the aforementioned recombinant viral vectors to humans and suppressing the onset of IDDM in humans or comprising inoculating an individual as a juvenile or infant with a coxsackievirus (which can be a virulent coxsackievirus such as CVB3. The claimed compositions are recited as being for treatment of humans and the specification indicates that the only disclosed use for the claimed compositions is for treatment of IDDM in humans *in vivo* and therefore the claims will be examined as therapeutic compositions.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is needed is not based upon a single factor, but is a

conclusion reached by weighing many factors. (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir). These factors include the following:

1) Unpredictability of the art. The art in the area of treatment of IDDM (an autoimmune disease) in humans using recombinant coxsackieviral vectors or coxsackieviruses is highly unpredictable. The factors underlying the development of IDDM in humans are complex and poorly understood and involve the genetic make-up of the individual, environmental factors, individual host factors which facilitate the transition from normal non-pathogenic autoreactivity to autoimmune disease, impaired peripheral tolerance due to abnormalities involving receptors or ligands that mediate down-regulation of lymphocyte activity, a bias to generate Th1 pro-inflammatory responses as opposed to more balanced Th1/Th2 responses, etc. Additionally, the role of enteroviral infections (such as coxsackievirus infections) in the development of IDDM in humans is far from clear (See for example, Graves et al., Diabetes, 1997, Vol. 46, pp. 161-168). Indeed, it is unclear if the individual must already be exhibiting autoimmunity for infection by enteroviruses such as coxsackieviruses to be involved in some fashion with precipitating IDDM. Also, it is unknown whether single or multiple infections of coxsackieviruses are required to in some fashion induce IDDM and whether coxsackievirus infection can trigger beta-cell autoimmunity in children.

With regard to recombinant viral vector compositions comprising attenuated coxsackieviral

genomes and sequences encoding one or more immunomodulatory proteins such as IL-4, it is noted that said vectors and methods of use of said vectors to treat, prevent or suppress the development of IDDM fall into the area of gene therapy. The gene therapy art is highly unpredictable. No experience has been accumulated using recombinant coxsackieviral based vectors to express transgenes *in vivo* in humans and the ability of said vectors to do so is untested. In order for applicants' invention to work, the coxsackieviral vector must infect the appropriate cells and express and secrete the appropriate immunomodulatory protein at the appropriate levels for extended periods to effect a treatment for IDDM. However, some of the major unsolved problems in gene therapy involve the *in vivo* targeting of the vectors to the appropriate cells or tissue and the unpredictable and transient expression of viral vector delivered transgenes in cells *in vivo* (for example, see Verma et al., Nature, 1997, Vol.389, pp. 239-242; Anderson et al., Nature, 1998, Vol. 392, pp. 25-30; Kmeic, American Scientist, 1999, Vol. 87, pp. 240-247 (all cited by applicants), etc.). Also, an additional complicating factor in gene therapy techniques is that the behavior of many viral gene therapy vectors in animal models is very different from how the viral vectors behave in humans (See for example, Fox, Nature Biotechnology, 2000, Vol. 18, pp. 143-144).

With regard to use of the claimed coxsackieviral vectors to prevent IDDM or suppress the onset of IDDM in humans, it is unclear how administration of these viruses or viral vectors

would serve to "vaccinate" an individual against IDDM or prevent the onset of IDDM. If the mechanism involved relates to inducing a host immune response to further infections by other coxsackieviruxes which somehow are IDDM inducing, then it is unclear, given applicants' specification, that the disclosed recombinant coxsackievirus vectors can induce immunity against other unrelated coxsackievirus strains which may be diabetogenic. It is noted that there are no effective vaccines against any enteroviruses (excluding poliovirus) (See Chapman et al., Current Topics in Microbiology and Immunology, 1997, pp. 227-258, cited by applicants). Also, with regard to applicants administration of **virulent coxsackieviruses** to juveniles or infants in an attempt to delay the onset of IDDM (claims 26-29), it is unclear how the skilled artisan would choose the individuals to be inoculated, i.e. would the individuals have to be screened in some fashion for the potential for developing IDDM? Also, it is unclear how applicants would practically use a method for delaying the onset of IDDM wherein the method involves the administration, to otherwise healthy children or infants, of a potentially lethal virus with a significant mortality rate (See for example, Tu et al., J. Virol., 1995, Vol. 69, No. 8, pp. 4607-4618, especially p. 4607, cited by applicants).

2) State of the art. The state of the art with regard to use of coxsackieviruses or recombinant coxsackieviral vectors to treat, prevent or delay the onset of IDDM in humans is nil. The state of the art regarding gene therapy is poorly developed with no definitive examples of success.

3) Number of working examples. Applicants present no working examples of the claimed invention.

4) Amount of guidance presented by applicants. Applicants present some data using non-obese diabetic mice (NOD mice) wherein administration of attenuated coxsackieviruses expressing IL-4 were able to suppress diabetes in NOD mice and administration of avirulent and especially virulent coxsackieviruses can delay the onset of diabetes in NOD mice. However, it is unclear how relevant the data obtained from NOD mice is to treatment of the human disease. Since the development of the human disease involves a complex interplay of many factors involving genetics, development of autoimmune symptoms, environment, etc., it is unclear how the use of a mouse model wherein the disease state in the mouse does develop in the same fashion as the disease state in the human can be used as a model to test for factors which can prevent or delay the onset of IDDM in humans.

5) Scope of the invention. The scope of the invention is broad with the broadest claims reading on use of any coxsackievirus strain to suppress the onset of IDDM in humans or the use of any viral vector comprising any attenuated coxsackievirus strain expressing any immunomodulatory agent to treat IDDM in humans.

6) Nature of the invention. The nature of the invention involves treatment of a complex, poorly understood, autoimmune disease in humans using gene therapy techniques involving

recombinant coxsackieviral vectors or administering coxsackieviruses to juveniles or infants.

7) Level of skill in the art. The level of skill in the art is high; however, given the unpredictability of the art, the lack of guidance presented by applicants, the complex nature of the invention and the poorly developed state of the art, the skilled artisan would have needed to have practiced essentially trial and error experimentation to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that the skilled artisan would have needed to have conducted undue and excessive experimentation in order to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 is vague in the recitation of the phrase "...comprises a a coxsackievirus B genome." Deletion of the second "a" after comprises would be remedial.

References crossed out by the examiner on the attached PTO-1449 form have not been considered because copies of said references have not been provided by applicants.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Faxes may be submitted directly to the examiner at (703) 746-5061.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David Guzo
November 18, 2002

DAVID GUZO
PRIMARY EXAMINER